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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/545,428	04/07/00	LEVESQUE M D	CEDAR-044526

EXAMINER	
SCHMIDT,M	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/545,428	Levesque et al.
Examiner	**Group Art Unit**
Schmidt	1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-27 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-27 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☒ Notice of References Cited, PTO-892

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

Part of Paper No. 3

*U.S. Government Printing Office: 1997 — 417-378/50309

DETAILED ACTION

1. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the European Patent Office on 01/20/2000 and in Japan on 01/20/2000. It is noted, however, that applicant has not filed a certified copy of the foreign applications as required by 35 U.S.C. 119(b).

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,087,168. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '428 introduce the following which are encompassed by the broad "comprising" language of the claims of '168: (1) the neurotrophins CNTF, PDGF and sonic hedgehog, and (2)

the physiological and/or immunological feature is nestin, neural RNA-binding protein Musashi, neurofilament M, neural-specific beta-tubulin, neural-specific enolase, microtubule associated protein 2, glial fibrillary acidic protein (GFAP), or O4. The claims of '428 also encompass broadly any transdifferentiated cell, methods of making or using, whereby the cell is transdifferentiated into a cell having one or more morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal, or glial cell. This breadth is also encompassed by the claims of '168 due to use of the open "comprising" language in those claims.

4.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 contains a typographical error in line 3. It appears "fro" should read "from."

Claim 11contains a typographical error in line 1. It appears "cells to cells into cells having" should read either "to cells" or "into cells."

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 5-12 and 15-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5-12 and 15-25 are drawn to a breadth of transdifferentiated cells, kits comprising said cells and cell cultures having a broad scope of morphological, physiological and/or immunological feature(s) of a neural progenitor, neuronal or glial cell.

The specification as filed teaches that human adult skin was cultured and transfected with pRcCMVneo vectors containing B-gal, NeuroD1, NeuroD2, hASH1, Zic1 or hMyT1 human genes. The specification teaches in example 3 the design of two antisense oligonucleotides to target human MSX1 and two antisense oligonucleotides to target human HES1. In example 4, the specification teaches the methods for detection of transdifferentiation of the epidermal cells to neural cells as immunohistochemical detection of neurofilament M, neural specific tubulin, neural specific enolase, microtubule associated protein 2, neurofilaments Mix, flial fibrillary acidic protein, and morphological criteria. The specification teaches that cells with neurites longer than three cell diameters (50 microns or longer) and expressing at least one neuronal marker were counted as neurons. Table 1 teaches the results of the transdifferentiation experiments showing

that a combination of neurogenic transcription factor expression coupled with decrease in MSX1 and HES1 expression was most effective at establishing transdifferentiation.

The claims encompass transdifferentiated neuronal cells made by different methods or having different physiological characteristics as described above. The specification however, only teaches in Table 1 a defined set of cells having some characteristic of a differentiated neuronal cell, the structure of which is not adequately described therein. The specification teaches broadly that different characteristics of neuronal cells were evaluated, but does not specify the uniformity of such characteristics amongst or between the cells having different transcription factors and antisense sequences applied. Therefore, it is not clear to one of skill in the art that the cells taught as differentiated neuronal cells have the structures as claimed or that a representative number of such cells was described by the specification as filed.

Further it is not clear from the specification as filed that the cells taught as having some or several such differentiation markers could be considered differentiated neuronal cells per se. The activation of one or several genes in epidermal cells leading to the transcription of one or more neuronal markers or a single physiological response does not indicate that such modified epidermal cells would necessarily have the function of neuronal cells based on cell acquisition of one or several such morphological features.

The claims drawn to kits containing ingredients for differentiation of epidermal cells to neuronal cells are further not adequately described by the specification as filed because the

specification does not teach the structures of the cells based on the application of the various kit components.

In summary, the claims are drawn to a genus of transdifferentiated neuronal cells having different characteristics yet the specification as filed does not teach the correlation of these characteristics to the methods applied for transdifferentiation of the epidermal cells. Therefore, while the cells may suggest specific neuronal features, they do not show possession of a representative number of such whole, complete, neuronal cells to show possession to one of skill in the art of the genus of differentiated neuronal cells as claimed.

9. Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for differentiated cells showing some specific neuronal cell features, does not reasonably provide enablement for the scope of methods for making neuronal cells as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-27 are drawn to methods of transdifferentiating an epidermal cell into a neuronal cells and the cells produced by said process.

The specification as filed teaches that human adult skin was cultured and transfected with pRcCMVneo vectors containing B-gal, NeuroD1, NeuroD2, hASH1, Zic1 or hMyT1 human genes. The specification teaches in example 3 the design of two antisense oligonucleotides to

target human MSX1 and two antisense oligonucleotides to target human HES1. In example 4, the specification teaches the methods for detection of transdifferentiation of the epidermal cells to neural cells as immunohistochemical detection of neurofilament M, neural specific tubulin, neural specific enolase, microtubule associated protein 2, neurofilaments Mix, flial fibrillary acidic protein, and morphological criteria. The specification teaches that cells with neurites longer than three cell diameters (50 microns or longer) and expressing at least one neuronal marker were counted as neurons. Table 1 teaches the results of the transdifferentiation experiments showing that a combination of neurogenic transcription factor expression coupled with decrease in MSX1 and HES1 expression was most effective at establishing transdifferentiation.

Claims 1 and 5 as written broadly encompasses any differentiated neuronal cell originating as a skin cell where a DNA encoding a neurogenic transcription factor is expressed and an antisense to a negative regulator of neuronal differentiation is expressed. The specification as filed however, only teaches differentiated cells having specific physical or marker characteristics of neuronal cells as a result of specific expression of neuronal transcription factors with and without antisense suppression (see Table 1).

This method of differentiation of epidermal cells to neuronal cells recites several key steps for achieving a cell having certain neuronal characteristics, but is unpredictable in the following instances:

The epidermal cell obtained from the patient is not specified as to type nor are any other physical characteristics given to determine the susceptibility of the cell to dedifferentiation, further, the specification as filed does not specify how the cells were dedifferentiated.

The specification teaches only expression of certain neurogenic transcription factors in combination with certain antisense oligonucleotides resulting in cells having a phenotypic or neurogenic marker expression. Specifically example 1 teaches a calcium-free medium for growth of the skin cell culture, but does not provide guidance for what other cytokines, growth factors or genetic manipulation (claim 2) would be necessary to dedifferentiate the cells.

In the case of antisense oligonucleotides to negative regulators of neuronal differentiation, there is a high level of unpredictability known in the antisense art for design of antisense molecules to known target genes (see Branch). The factors considered unpredictable are (1) delivery and stability of the antisense molecule, (2) availability of the intended target site, and (3) effective antisense action marked by a decrease in the intended target expression. The specification only teaches antisense to two genes, human MSX1 and human HES1. Therefore it would require 'trial and error' experimentation to design antisense molecules to other negative regulators of neuronal differentiation as claimed.

The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

In regards to the screening and diagnostic claims, the specification as filed teaches only prophetically methods of application for screening and therapeutic applications of the transdifferentiated cells of claims 1 or 5.

The specification as filed therefore does not provide any guidance for the transplantation of transdifferentiated cells/tissues into a patient nor does it provide any evidence of the cells ability to form functional connections and operate as true neurons either *in vitro* or in a whole organism.

The factors considered unpredictable for such treatment would include the ability of the cells to retain the transdifferentiated state, for example the antisense inhibition of the transdifferentiated cells would alone present a high level of unpredictability. There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important

sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the therapeutic claims read broadly on administration of an antisense inhibitor in any transdifferentiated cell to a whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in

whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Further, no guidance is taught by way of example for assaying the effect of the potential new drugs on a physiological or molecular biological property of said transdifferentiated neuronal cells. The only physiological or molecular biological properties taught are those characteristics applied to determination of the neuronal status of the transdifferentiated cells such as morphological occurance of a neurite and immunological expression of neuronal antigens.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader* may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. M. Schmidt
November 20, 2000

REMY YUCEL, PH.D
PRIMARY EXAMINER